Supplementary Table 1. Exome Sequencing Quality Statistics for Cases and Controls

Category	Cases (Mean ± 95% CI)	Controls (Mean ± 95% CI)
Read length (bp)	74	74
Number of reads per sample (M)	65.7 ± 1.9	106.7 ± 2.1
Median independent reads at each targeted base (X)	51.9 ± 1.3	78.2 ± 1.4
Mean independent reads at each targeted base (X)	63.5 ± 1.6	98.5 ± 1.9
Percent of targeted bases with ≥8 independent reads	93.3 ± 1.8	95.3 ± 0.1

Supplementary Table 2. Sequencing Coverage of *PARN* and *RTEL1* in Cases and Controls

	Cases		Controls	
	PARN **(Mean ± 95% CI)**	***RTEL1*** **(Mean ± 95% CI)**	***PARN*** **(Mean ± 95% CI)**	***RTEL1*** **(Mean ± 95% CI)**
Mean independent reads per base (X)	117.9 ± 3.6	29.4 ± 1.4	165.0 ± 3.4	65.8 ± 1.5
Percent of bases with ≥8 independent reads	100.0 ± 0.0	95.0 ± 0.8	99.7 ± 0.2	98.2 ± 0.2

Supplementary Table 3. Burden of Novel Variants in Familial Pulmonary Fibrosis Cases and Controls of European descent

YCGA controls	Alleles, Damaging				
	Controls		Cases		p-value
Gene	# variant	# reference	# variant	# reference	
PARN	0	5632	5	151	1.33E-08
RTEL1	0	5602	2	154	7.29E-04
KIF15	0	5632	2	154	7.40E-04
ZNF14	1	5631	2	154	2.13E-03
ARAP2	1	5631	2	154	2.13E-03
COL23A1	1	5631	2	154	2.13E-03
LRRK2	1	5631	2	154	2.13E-03
STAB2	1	5631	2	154	2.13E-03
PRIM2	2	5630	2	154	4.18E-03
FBXL4	2	5630	2	154	4.18E-03
DNAH7	7	5625	2	154	2.30E-02
FAM48A	0	5632	1	155	2.70E-02
MLL3	0	5632	1	155	2.70E-02
SLC43A2	0	5632	1	155	2.70E-02
NAF1	0	5632	1	155	2.70E-02
GLIPR1L2	0	5632	1	155	2.70E-02
FAM75C2	0	5632	1	155	2.70E-02
DSE	0	5632	1	155	2.70E-02
ADAMTSL1	0	5632	1	155	2.70E-02
ALPI	0	5632	1	155	2.70E-02

YCGA controls	Alleles, damaging plus missense at conserved positions				
	Controls		Cases		p-value
Gene	# variant	# reference	# variant	# reference	
RTEL1	4	5598	5	151	1.58E-06
PARN	11	5621	6	150	3.37E-06
STK11IP	3	5629	3	153	3.62E-04
ELMOD1	0	5632	2	154	7.22E-04
NEU4	0	5632	2	154	7.22E-04
KIF15	5	5627	3	153	9.74E-04
OPA1	5	5627	3	153	9.74E-04
CNTN5	5	5627	3	153	9.74E-04
PRIM2	6	5626	3	153	1.43E-03
FLT1	6	5626	3	153	1.43E-03
TOM1L2	6	5626	3	153	1.43E-03
MAP3K2	6	5626	3	153	1.43E-03
UBAP2L	6	5626	3	153	1.43E-03
KIAA1671	7	5625	3	153	2.01E-03
CACNB4	7	5625	3	153	2.01E-03
ZNF14	1	5631	2	154	2.13E-03
FAM48A	1	5631	2	154	2.13E-03
MLL3	1	5631	2	154	2.13E-03
SLC43A2	1	5631	2	154	2.13E-03
TAS1R3	1	5631	2	154	2.13E-03

Supplementary Table 4. Burden of Variants with a Minor Allele Frequency < 0.1% in Familial Pulmonary Fibrosis Cases and Controls of European descent

YCGA controls	Alleles, Damaging				
	Controls		Cases		p-value
Gene	# variant	# reference	# variant	# reference	
PARN	0	5632	5	151	1.33E-08
MPZL3	0	5632	2	154	7.22E-04
RTEL1	0	5602	2	154	7.29E-04
ECT2L	9	5623	3	153	3.53E-03
PRIM2	2	5630	2	154	4.18E-03
TRIM22	2	5630	2	154	4.18E-03
FBXL4	2	5630	2	154	4.18E-03
LRRK2	2	5630	2	154	4.18E-03
CCDC141	2	5630	2	154	4.18E-03
COL23A1	2	5630	2	154	4.18E-03
ARAP2	2	5630	2	154	4.18E-03
ZNF14	3	5629	2	154	6.84E-03
KPTN	3	5629	2	154	6.84E-03
CYP4B1	3	5629	2	154	6.84E-03
KIF15	4	5628	2	154	1.01E-02
TINAG	4	5628	2	154	1.01E-02
SRGAP2	5	5627	2	154	1.39E-02
STAB2	7	5625	2	154	2.30E-02
ZNF776	7	5625	2	154	2.30E-02
FAM48A	0	5632	1	155	2.70E-02

YCGA controls	Alleles, damaging plus missense at conserved positions				
	Controls		Cases		p-value
Gene	# variant	# reference	# variant	# reference	
PARN	21	5611	6	150	3.37E-06
RTEL1	14	5588	5	151	1.17E-04
MYO10	12	5620	4	152	7.18E-04
SDHC	0	5632	2	154	7.22E-04
CAV3	5	5627	3	153	9.74E-04
ID1	6	5626	3	153	1.43E-03
TOM1L2	7	5625	3	153	2.01E-03
ADORA3	7	5625	3	153	2.01E-03
NKIRAS1	1	5631	2	154	2.13E-03
HSPA5	1	5631	2	154	2.13E-03
FAM48A	1	5631	2	154	2.13E-03
C14orf101	1	5631	2	154	2.13E-03
MAP3K2	18	5614	4	152	2.54E-03
REPS1	8	5624	3	153	2.70E-03
UBAP2L	9	5623	3	153	3.53E-03
PRIM2	9	5623	3	153	3.53E-03
IARS	20	5612	4	152	3.54E-03
ZCCHC5	2	5630	2	154	4.18E-03
TRIM22	2	5630	2	154	4.18E-03
TLR8	2	5630	2	154	4.18E-03

Supplementary Table 5. Increased number of novel variants in *PARN* and *RTEL1* in familial pulmonary fibrosis probands vs. controls of European descent

YCGA controls	Number of Individuals with Damaging plus Conserved Missense Alleles					Number of Individuals with Damaging Alleles				
	Controls		Cases		p-value	Controls		Cases		p-value
Gene	Variant	Reference	Variant	Reference		Variant	Reference	Variant	Reference	
PARN	**11**	**2805**	**6**	**72**	**3.09E-06**	**0**	**2816**	**5**	**73**	**1.25E-08**
RTEL1	**4**	**2797**	**5**	**73**	**1.49E-06**	**0**	**2801**	**2**	**76**	**7.25E-04**

NHLBI controls	Number of Individuals with Damaging plus Conserved Missense Alleles					Number of Individuals with Damaging Alleles				
	Controls		Cases		p-value	Controls		Cases		p-value
Gene	Variant	Reference	Variant	Reference		Variant	Reference	Variant	Reference	
PARN	**8**	**4292**	**6**	**72**	**7.06E-08**	**0**	**4300**	**5**	**73**	**1.58E-09**
RTEL1	**6**	**4294**	**5**	**73**	**6.71E-07**	**2**	**4298**	**2**	**76**	**1.84E-03**

YCGA controls, variants analyzed from Yale Center for Genome Analysis; NHLBI, variants from NHLBI ESP database

Supplementary Table 6. Clinical Features of Individuals in *PARN* and *RTEL1* Familial Pulmonary Fibrosis Kindreds.

Gene	Family	Subject	FVC (%)	FEV_1 (%)	FEV_1/ FVC	DL_{CO} (%)	WBC, $X10^3$/uL	Hgb g/dL	MCV fL	Plt $X10^3$/uL	Clinical Features
PARN	F349/F373	III.4									Tuberculosis, as per family
PARN	F349/F373	IV.2									Pulmonary fibrosis, as per family
PARN	F349/F373	IV.3									Emphysema, as per family
PARN	F349/F373	IV.5									Pulmonary fibrosis, as per family. Life-long chicken farmer, on O_2 for last months of life
PARN	F349/F373	IV.7									Non-smoker. Carpenter x 10 years. Died 6 years after the diagnosis of pulmonary fibrosis was made. Autopsy with advanced UIP and biventricular hypertrophy.
PARN	F349/F373	V.1									38 pack-year history of smoking. Worked as a welder and farmer, required supplemental oxygen. Died of progressive pulmonary fibrosis with an obstructive component.
PARN	F349/F373	V.4	44	61	93	42	6.8	14.9	108 (H)	202	Cigar smoker. Rales on exam. CT chest with peripheral interstitial fibrosis, honeycombing and diffusely scattered regions of air trapping. Elevated RF; treated with azathioprine and cyclophosphamide without improvement. Died of progressive pulmonary fibrosis.
PARN	F349/F373	V.6	33	36	82	54	5.5	14	95.3	209	Never smoker. Chronic cough with dyspnea, rales and squeaks on exam, requiring supplemental oxygen. ILD thought secondary to Sjogren's syndrome, with sicca symptoms, ANA 1:320 and grade IV chronic sialadenitis on salivary gland biopsy. CT chest with diffuse peripheral areas of thick interlobular septa, ground glass opacities, honeycombing and air trapping. Treated with prednisone, mycophenolate, cyclophosphamide and rituximab with progression of lung disease.
PARN	F349/F373	V.7	56	63	88	30	13.8	11.0 (L)	97.2	530	Never smoker. Raised up to 250,000 chickens per year for 25 years. Chronic cough with dyspnea, rales and clubbing on exam, required supplemental oxygen. CT chest with peripheral, lower lobe predominant pulmonary fibrosis. Died 5 years after initial diagnosis of pulmonary fibrosis from respiratory insufficiency.
PARN	F70	II.1									Emphysema and liver disease, as per family
PARN	F70	II.4									Unknown lung disease and liver cirrhosis, as per family.
PARN	F70	II.7					12.7	11.2 (L)	95.8	189	CXR with pulmonary fibrosis. Dyspnea requiring chronic supplemental oxygen. ECHO with elevated RVSP. Died 6 years after initial diagnosis of pulmonary fibrosis with progressive dyspnea.
PARN	F70	II.8	58	71	94	20	9.5	14		192	Never smoker. Cattle and swine farmer for 45 years. Chronic cough and dyspnea, required supplemental oxygen. CT chest with severe fibrosis and honeycombing. Died of respiratory failure 9 years after initial diagnosis of pulmonary fibrosis.
PARN	F70	II.9					9.3	10.7 (L)	99.2 (H)	259	Worked as a millwright and welder for decades. Chronic cough, required supplemental oxygen. Surgical lung biopsy consistent with fibrosis. Heart catheterization with pulmonary hypertension. Treated with prednisone, methotrexate and cyclophosphamide with disease progression. Died 2 years after diagnosis of pulmonary fibrosis from acute respiratory failure.
PARN	F70	III.5					5.6	14			44 pack-year smoking history. Construction worker. Diagnosed with COPD with CT chest showing peripheral cystic changes and interstitial lung fibrosis within the upper lobes. ECHO with elevated RVSP. History of spina bifida occulta.
PARN	F70	III.6	34	34	77	28	6.2	13.8	96.1	161 (L)	8 pack-year smoking history. Cough, dyspnea, rales and clubbing on exam, required supplemental oxygen. ECHO with elevated RVSP. Surgical lung biopsy with UIP. Patient underwent lung transplantation 4 years after initial diagnosis of pulmonary fibrosis.
PARN	F416	I.2									Pulmonary fibrosis, as per family
PARN	F416	II.1									Pulmonary fibrosis and premature graying, as per family
PARN	F416	II.2									Pulmonary fibrosis, as per family
PARN	F416	II.3									7 pack-year smoking history. Farmer for 15 years. Chronic cough and dyspnea. Pulmonary fibrosis diagnosed by chest imaging as per patient. Premature graying
PARN	F416	II.4	61	72	86	50	6.0	13.1	104 (H)	334	Never smoker. Farmer for 40 years. Bilateral lung transplantation 3 years after diagnosis of

											pulmonary fibrosis.
PARN	F416	II.5									Pulmonary fibrosis, as per family
PARN	F32	II.1									Farmer. Pulmonary fibrosis, as per family
PARN	F32	II.3									Lung cancer, as per family
PARN	F32	III.1									20 pack-year smoking history. Dyspnea, rales on exam, required supplemental oxygen. Surgical lung biopsy consistent with UIP. Died 6 years after initial diagnosis of pulmonary fibrosis.
PARN	F32	III.2									Died of respiratory insufficiency. Autopsy consistent with UIP.
PARN	F436	I.1									Pulmonary fibrosis, as per family
PARN	F436	II.1									Unspecified lung disease, as per family
PARN	F436	III.1									Cigar smoker for 42 years. Diagnosis of sarcoidosis by lung biopsy.
PARN	F436	III.2	52	62	91	58	6.2	14.3	92.7	226	27 pack-year smoking history. Chronic cough, wheezing, dyspnea, rales on exam. CT chest with coarse reticulations and honeycombing. Progressive decline of pulmonary function, requiring supplemental oxygen.
PARN	F432	II.3									Life-long smoker, "Black lung disease", as per family
PARN	F432	II.4									Life-long smoker, worked in a feed mill, unspecified lung disease, as per family
PARN	F432	II.5									Life-long smoker, worked in a feed mill, unspecified lung disease, as per family
PARN	F432	III.1									Smoker, chronic cough, worsening dyspnea after elective knee replacement, pulmonary fibrosis, as per family
PARN	F432	III.2	61	73	93	13.2	9.4	13.6	89.6	297	Never smoker. Chicken and pigeon breeder. Dyspnea, wheezing, rales and clubbing on exam, requiring supplemental oxygen. CT chest with peripheral septal reticulations and honeycombing, transbronchial lung biopsy with granulomas. Treated with prednisone, imuran, mycophenolate with progression of lung disease. Died of respiratory insufficiency.
RTEL1	F415	II.3	64	67	78	16	6.5	12.6	95.4	192	60 pack-year smoking history. Worked as a railroad engineer for 40 years. Chronic cough, dyspnea, rales on exam, CT chest with peripheral reticulations with honeycombing, ECHO with elevated RVSP. Died of respiratory failure secondary to influenza pneumonia and progressive pulmonary fibrosis 2 years after initial diagnosis.
RTEL1	F415	II.4	53	52	75	34	10.2	11.1	83.7	311	10 pack-year smoking history. Chronic cough, wheezing, dyspnea, multiple respiratory illnesses, requiring supplemental oxygen. CT chest with air trapping and reticulations localized to the right middle and right lower lobes. ANA 1:80, elevated anti-Scl-70, treated with prednisone.
RTEL1	F415	III.2									Died of pulmonary embolism, as per family
RTEL1	F415	IV.1	63	63	82	27	9.6	10.9	89	285	Never smoker. Cough, dyspnea, rales on exam. Surgical lung biopsy consistent with NSIP. Treated with cellcept.
RTEL1	F343	I.2									Emphysema, died of pulmonary embolism, as per family
RTEL1	F343	II.2									Pulmonary fibrosis and lung cancer, as per family
RTEL1	F343	II.3	66	70	84		9.4	11.3	98.4	344	Smoker, as per family. On supplemental oxygen. Surgical lung biopsy with end-stage pulmonary fibrosis. Later diagnosed with moderately differentiated squamous cell lung carcinoma and treated with chemotherapy. Died of respiratory insufficiency.
RTEL1	F343	II.4	71	80	84	46	6.4	12.2	99.8	369	Nonsmoker. Chronic cough, dyspnea. CT chest with peripheral reticulation. Stable pulmonary function testing for 9 years.
RTEL1	F343	III.2	62	66	81	31	6.6	15.8	104 (H)	121	38 pack-year smoking history. Household bird exposures x 21 years, Chronic cough, dyspnea, rales on exam, required supplemental oxygen. Surgical lung biopsy with extensive fibrosing interstitial lung disease with small lymphoid aggregates. Died of hypoxic respiratory failure 3 years after initial diagnosis of pulmonary fibrosis.
RTEL1	F343	III.7	49	50	79	34	11.9	18	95	273	80 pack-year smoking history. Cement mason for 30 years, household bird for 24 years. Chronic cough, dypsnea, rales and clubbing on exam. Surgical lung biopsy with UIP. Also has a history of pulmonary embolism. Requires supplemental oxygen.
RTEL1	CKG351	I.2									Surgical lung biopsy with UIP with superimposed organizing pneumonia.
RTEL1	CKG351	II.1	49	59	92	10	10.9	13.9	94	303	Never smoker, chronic cough, rales on exam, requiring supplemental oxygen. CT with peripheral reticulations and honeycombing. Also with pulmonary hypertension by right heart

											catheterization. Died 1 year after diagnosis of progressive respiratory insufficiency.
RTEL1	F337	I.1									Pulmonary fibrosis, as per family report
RTEL1	F337	II.1	35	48	94		7.3	15.3	92	259	10 pack-year smoking history. Chronic cough, dyspnea, required supplemental oxygen. Surgical lung biopsy with UIP. Died 1 month after diagnosis of progressive respiratory insufficiency.
RTEL1	F337	II.3	46	54	82		12.1	14.9	104 (H)	176	Never smoker. Chronic cough, dyspnea, rales and clubbing on exam, requiring supplemental oxygen. Surgical lung biopsy with UIP with granulomas. Treated with prednisone and imuran. Also with hemochromatosis as per patient report. Died 3 years after diagnosis of pulmonary fibrosis from progressive disease.
RTEL1	CKG571	II.2									Pulmonary fibrosis and pancreatic cancer, as per family
RTEL1	CKG571	II.3									Pulmonary fibrosis, as per family
RTEL1	CKG571	III.2									Pulmonary fibrosis, as per family
RTEL1	CKG571	IV.1	30	34	92	19	5.6	14.9	94	248	92 pack-year smoking history. Worked as a bricklayer for 30 years. Chronic cough, dyspnea, rales and clubbing on exam, required supplemental oxygen. Surgical lung biopsy with severe interstitial fibrosis. Died 2.5 years after the initial diagnosis of pulmonary fibrosis from progressive disease.

Supplementary Table 7. PCR conditions and Primer Sequences for Sanger Sequencing of *PARN* and *RTEL1* Variants.

Gene	DNA Change	Impact	Forward Oligonucleotide	Reverse Oligonucleotide	Size (bp)	[Mg^{2+}] (mM)	Annealing Temp (^oC)
PARN	IVS4 -2a>g	Splice	cagtttggcctttgcacttt	CAAATTTGACATCTGGTGAGGA	199	1.5	50
PARN	c.529 C>T	Gln177*	TGATGAAAAACGTTCACAGG	gccattcacaacatcacacc	240	1.5	50
PARN	c.563_564insT	Ile188fs	cccaaagtgctgggattcta	ggacatgcagaaatgttcagg	298	1.5	50
PARN	c.751delA	Arg251fs	actccagcctgagcaacaag	aggtttttctgccaattcca	310	1.5	50
PARN	IVS16 +1g>a	Splice	tcataattctttgcttcgtggtt	tacggtctccagagccattc	196	2.5	50
PARN	c.1262 A>G	Lys421Arg	ggtctgaactttcaggcttgg	cccaataactccaaactgacatc	222	1.5	50
RTEL1	c.602delG	Gly201fs	agaccctcagtgggtgcttt	tcagagctgcttaaacttttcg	388	1.5	50
RTEL1	c.1451 C>T	Pro484Leu	GGAAGGTGCTGAGCTACTGG	gacccccaccacttccac	207	1.5	50
RTEL1	c.1940 C>T	Pro647Leu	tgacccacagatggagctt	TGCCCAGAGAGGAActgtg	392	1.5	50
RTEL1	c.2005 C>T	Gln693*	tgacccacagatggagctt	TGCCCAGAGAGGAActgtg	392	1.5	50
RTEL1	c.3371 A>C	His1124Pro	CTGCTGCACAgcaagtgg	GAGCCCTGTGGGTAAGCA	248	2.5	55
RTEL1	c.3528 G>C	Lys1176Asn	ctgggagtgagcagcaaag	AGGCTCACCCCACTCAGAT	217	1.5	55

Intron sequences are indicated by lowercase letters; exon sequences are indicated by uppercase letters. All primers are listed from 5' to 3'.

PCR Buffer Conditions: 1X PCR buffer (Applied Biosystems), $MgCl_2$ at the concentration listed above, 0.2 mM dNTPs, 0.25 μM each primer, 50 ng genomic DNA, 1 U ABI Taq polymerase. PCR Cycling Conditions: 95^{o}C for 5 min; at least 30 cycles of 94^{o}C for 15 sec, annealing temperature as listed above for 15 sec, 72^{o}C for 30 sec; followed by 72^{o}C for 10 min.